First-Round Peer Review

Reviewer A

Comment 1: The authors identify an important clinical question whose answer has significant implications for surgeons seeking to risk-stratify patients and provide appropriate counseling prior to definitive treatment for pulmonary malignancies. The study population is thoughtfully focused, and the data they gather on their subjects is rich and relevant for this question, namely the extent of surgical disease, pathologic findings, and pulmonary comorbidities. This is a strength. The principal shortcoming relates to an inherent peculiarity of the outcome, i.e., it is rare (0.5%); the authors judiciously approach this problem with clinical sanguinity by examining the univariable tabulation across a multitude of potential associated factors, and then using the subset analysis to drive more forceful conclusions regarding this association. There are two ways this shortcoming needs to be addressed. The first is by defining a modeling approach with respect to the peculiarity noted above, then by comparing estimates and (if necessary) conclusions across different modeling approaches (references below).
Please provide justifications for using logistic regression, selection of predictor(s), and consideration of BPF as a rare outcome.
Please compare estimates obtained with those using alternative methods (penalized logistic regression, for example), for stability.

Reply 1: Thank you for your insightful comments. I completely agree with you that the shortcoming relates to the low number of events. Although events per variables >10 is a common criterion, the literature you gave me has shown that events per variables have a weak correlation with predictive accuracy. Following your recommendation, the reliability of the results was assured by conducting subgroup analyses and by comparing the estimates and variables selected by lasso regression analysis with the results of logistic regression analysis. In the lasso regression with $\lambda = 0.02$, three variables were selected that were significantly associated factors in the logistic regression analysis.

Changes in the text 1:

I have changed the results of multivariable analysis in the subgroup of male patients after right lower lobectomy (Table 4).

I have added the comparison of the estimates obtained by logistic regression analysis and lasso regression analysis (Table 5).

I have added the following sentence to the Methods section (page 5, line 122):

The factors associated with the development of BPF were analyzed by performing multivariable logistic regression and lasso regression analyses using covariates with P value <0.1 in univariable analysis. The statistical analyses were performed in the R software environment (version 4.0.3; the R Foundation for Statistical Computing, Vienna, Austria).

I have added the following sentence to the Results section (page 7, line 158):

The multivariable logistic regression analysis revealed that high serum C-reactive protein levels (odds ratio = 1.83, 95% CI = 1.17–2.87, P = 0.009) and a history of gastric cancer surgery (odds ratio = 5.52, 95% CI = 1.06–28.8, P = 0.042) were significantly associated with the development of BPF in men who underwent right lower lobectomy (Table 4). Conversely, bronchial stump coverage was inversely associated with the development of BPF (odds ratio = 0.06, 95% CI = 0.00–0.77, P = 0.031). Table 5 presents the estimates obtained by logistic regression analysis and lasso regression analysis. Three variables were selected using lasso regression with λ = 0.02 that were significantly associated with BPF in the logistic regression analysis.

I have added the following sentence to the Discussion section (page 9, line 225):

Furthermore, considering that only 14 relevant cases were recorded, the predictive performance of the multivariable logistic regression analysis might have been hampered. A larger, multi-institutional study should be conducted in the future. Although events per variables of >10 is a common criterion, some studies have shown that events per variables have a weak correlation with predictive accuracy (25). In this study, the reliability of the results was ensured by conducting subgroup analyses and comparing the results obtained by lasso regression analysis with the results of logistic regression analysis.

Comment 2: Please include confidence intervals (or calculated errors) for all point estimates reported in the text (lines 152, 154).

Reply 2: Thank you for your careful review. I have added confidence intervals for all point estimates.

Changes in the text 2:
Page 6, line 146
Multivariable logistic regression analysis using eleven variables revealed that having a history of gastric cancer surgery (odds ratio = 7.02, 95% confidence interval [CI] = 1.25–39.6, P = 0.027) and high serum C-reactive protein levels (odds ratio = 1.61, 95% CI = 1.02–2.55, P = 0.040) were significantly associated with the development of BPF (Table 2). The odds ratios for male sex and right lower lobectomy were infinite.
Page 7, line 158
The multivariable logistic regression analysis revealed that high serum C-reactive protein levels (odds ratio = 1.83, 95% CI = 1.17–2.87, P = 0.009) and a history of gastric cancer surgery (odds ratio = 5.52, 95% CI = 1.06–28.8, P = 0.042) were significantly associated with the development of BPF in men who underwent right lower lobectomy (Table 4). Conversely, bronchial stump coverage was inversely associated with the development of BPF (odds ratio = 0.06, 95% CI = 0.00–0.77, P = 0.031).

Reviewer B

It is clearly written and examines an important topic of BPF occurrence in lobectomy, which has not been explored as deeply as after advanced resections. The findings of right lower lobe breakdown particularly in patients with risk for aspiration makes clinical sense. I have a few questions for you to address:
Comment 1: Was a multivariate analysis done for the main cohort (before excluding women and lobectomies other than lower lobectomy)? What were the findings?
Reply 1: Thank you for your careful review. Following your suggestion, I have added the results of the logistic regression analysis for the total cohort (Table 2). Multivariable analysis revealed that having a history of gastric cancer surgery (odds ratio = 7.02, 95% confidence interval [CI] = 1.25–39.6, P = 0.027) and high serum C-reactive protein levels (odds ratio = 1.61, 95% CI = 1.02–2.55, P = 0.040) were significantly associated with the development of BPF. The odds ratios for male sex and right lower lobectomy were infinite.

Changes in the text 1:

I have added Table 2 and the following sentences in the Results section (page 6, line 146).

Multivariable logistic regression analysis using eleven variables revealed that having a history of gastric cancer surgery (odds ratio = 7.02, 95% confidence interval [CI] = 1.25–39.6, P = 0.027) and high serum C-reactive protein levels (odds ratio = 1.61, 95% CI = 1.02–2.55, P = 0.040) were significantly associated with the development of BPF (Table 2). The odds ratios for male sex and right lower lobectomy were infinite.

Comment 2: Does the author's institution have a higher incidence of gastric cancer/resections than would be expected globally? How does this influence the results?

Reply 2: As you pointed out, the proportion of patients with a history of gastric cancer surgery (3%) was higher than globally expected. In Japan, the prevalence of gastric cancer among men in their 70s is about 1%, while in western countries it is about 1/10 to 1/5 of that in Japan. Our institution is a cancer center where more than 500 gastric cancer surgeries per year were performed. Institutional specificities may have caused the high prevalence of gastric cancer in our study. Although it is certain that the risk of BPF is higher in patients with a history of gastric cancer surgery, no statistically significant difference might have been found if the study was conducted in a population with low prevalence of gastric cancer.

Changes in the text 2:

I have added the following sentences in the Discussion section (page 9, line 221).

The proportion of patients with a history of gastric cancer surgery (3%) was higher than globally expected. The regional and institutional specificities might have contributed to the high prevalence of gastric cancer in this study cohort. If the study was conducted in a population with low prevalence of gastric cancer, no statistically significant difference might have been found.

Comment 3: If subcarinal lymph node dissection has previously been shown to be related to BPF formation, does this contribute to the RLL BPF rate observed here? Should the technique be changed?

Reply 3: In the subgroup of male patients after right lower lobectomy, 75% of the patients

underwent subcarinal lymph node dissection. The risk for BPF was not significantly different between patients with and without subcarinal lymphadenectomy (4.5% vs. 3.6%, P = 0.72) in this study.

Changes in the text 3:
I have added the following sentences in the Results section (page , line).
The risk for BPF was not significantly different between patients with and without subcarinal lymphadenectomy (4.5% vs. 3.6%, P = 0.72).

Comment 4: How many and why were muscle flaps used in this series?

Reply 4: As shown in Table 1, 195 (6.1%) patients underwent bronchial stump coverage to prevent BPF; intercostal muscle flaps were used in 137 cases and pericardial fat pad in 58 cases. Intercostal muscle flaps were often selected in patients at high risk of BPF.

Changes in the text 4:
I have added the following sentences in the Results section (page 6, line 133).
Of 195 (6.1%) patients who underwent bronchial stump coverage, intercostal muscle flaps and pericardial fat pads were used in 137 and 58 patients, respectively.

Second-Round Peer Review

Reviewer A

Comment 1: I defer to the expertise of the clinical reviewers, but could the authors briefly discuss the pathway for how a history of gastric cancer affects BPF risk?

Reply 1: Thank you for your careful review. The reasons why a history of gastric cancer surgery is associated with the development of BPF are discussed in the Discussion section (line 217-224) as follows. Although not proven, low nutrition and subclinical aspiration may be involved.
In this study, history of gastric cancer surgery was significantly associated with the development of BPF. Our previous study had revealed that upper gastrointestinal surgery was

an independent factor associated with postoperative pulmonary complications after lung cancer surgery (24). Generally, surgery for upper gastrointestinal cancer can have a profound effect on postoperative nutritional status (25). Nutritional status may have some influence on the risk of BPF. Moreover, regurgitation of gastrointestinal contents following upper gastrointestinal surgery may have caused aspiration pneumonia and increased the risk of developing BPF.

Comment 2: Please include a reference for lasso regression, including a brief description for the reader (typically capitalized) including the specific R packageas well as a justification.

Reply 2: Thank you for your comment. I have added a reference for lasso regression including a brief description and the specific R package.

Changes in the text 2:
Page 6, line 126
The factors associated with the development of BPF were analyzed by performing multivariable logistic regression and least absolute shrinkage and selection operator (LASSO) regression analyses (18) using covariates with P value <0.1 in univariable analysis. LASSO regression is one of the regularized regression models and minimizes the residual sum of squares subject to the sum of the absolute value of the coefficients being less than a constant. LASSO regression is a method that allows the selection of only those explanatory variables that influence the objective variable. The statistical analyses were performed in the R software environment (version 4.0.3; the R Foundation for Statistical Computing, Vienna, Austria). LASSO regression was performed using the "glmnet" package.